Original Research Paper

Volume-9 | Issue-1 | January-2019 | PRINT ISSN - 2249-555X

Gynecology

MIFEPRISTONE IN THE MEDICAL MANAGEMENT OF UTERINE FIBROIDS

Dr. Alakananda Professor, Department of Obstetrics and Gynecology, Gauhati Medical College and Hospital, Assam, India

Dr.B.Basumatary* Associate Professor, Department of Obstetrics and Gynecology, Gauhati Medical College and Hospital, Assam, India*Corresponding Author

Dr.B.Sreeja Reddy Postgraduate trainee, Department of Obstetrics and Gynecology, Gauhati Medical College and Hospital, Assam, India

ABSTRACT Leiomyoma is the common benign tumor of uterus with maximum incidence between 35-45 years of age.It is a common indication for hysterectomy in India. An effective medical treatment option may reduce hysterectomy and associated morbidity. So this study was conducted to evaluate the effect of low dose mifepristone on uterine fibroids. Methodology : A total of 50 patients with symptomatic fibroids were enrolled in this hospital based prospective study. Hemogram, liver function tests, ultrasound and endometrial histology was performed. Patients were given oral Mifepristone 25mg/day for 3 months and followed at 3 and 6 months. Results and Observations: Mean myoma volume decreased by 30.69% at 3 monthsand 42.49% at 6 months. Mean uterine volume decreased by 17.39% at 3 months and 16.54% at 6 months. 34% patients showed endometrial thickness≥10mm after the treatment. Mean PBAC score reduced by 96.53% at 3 months and 65.83% at 6 months. Mean VAS for dysmenorrhea reduced by 81.18% at 3 months and 29.7% at 6 months. 84.61% developed amenorrhoea at the end of 3 months. No major side effects were noted during the course of the study. Conclusions: Our study concluded that low-dose mifepristone is useful in case of symptomatic moderate sized leiomyoma.

KEYWORDS : Leiomyoma – PBAC – VAS - Amenorrhoea – fibroid volume – mifepristone – medical management.

INTRODUCTION:

Uterine leiomyoma are commonest benign gynaecological tumours occurring in upto 25 percent of women in reproductive age and about 40 percent have symptoms severe enough to warrant therapy. 1 Definitive treatment for symptomatic myomas has always been surgical and myomas accounts for 40 percent of all hysterectomies in premenopausal women.2. Symptoms include menstrual disturbances, commonly menorrhagia and dysmenorrhoea, pressure symptoms such as increased urinary frequency, pelvic pain and constipation, and they may interfere with reproduction3 by causing subfertility or preterm birth depending upon the location of fibroid. Except hysterectomy, no surgical treatment provides a complete cure, which is not applicable to all. As such there is clearly a need for medical therapy that eliminates the need for surgery. One such drug which has an effect as an antiprogestin is Mifepristone or RU 486.

It is a 19 nor steroid with antiprogesterone and antiglucocorticoid activity4. Direct suppressive effects on endometrial vasculature as well as reducing stromal VEGF has been suggested for reducing menstrual blood loss5.

MATERIALS AND METHODS :

This was a hospital based prospective study conducted in the Department of Obstetrics and Gynaecology, Gauhati Medical College and Hospital, Guwahati from 1st july 2017 to 30th june 2018 .

INCLUSION CRITERIA :

i. Women with symptomatic fibroids < 10cm
ii. Without any endometrial hyperplasia with atypia

EXCLUSION CRITERIA :

I. Women presenting with severe anemia (hemoglobin <7gm/dl) & acute symptoms like sudden heavy menstrual bleeding

ii. On hormonal medication within 3 months of starting the treatment or on corticosteroids

iii. History of breast cancer or other genital malignancies

iv. Pelvic inflammatory disease

v. Pregnancy

vi. Suspicion of leiomyosarcoma on ultrasound examination

vii. Severe renal or hepatic dysfunction
viii. D & C report showing endometrial hyperplasia with atypia

Informed consent was taken from all the patients before including them in the study. Detailed history was taken regarding the socio-demographic profile including age, socio-economic status , parity and menstrual history. Average blood loss was estimated using Pictorial Blood loss Assessment Chart(PBAC). The degree of dysmenorrhea and abdominal pain was estimated using Visual Analog Scale(VAS) score. All patients were clinically examined and baseline blood investigations like hemoglobin, liver function tests, serum creatinine were done . Trans abdominal ultrasound using 5MHz probe of Mindray machine was done to look for uterine volume, fibroid volume, endometrial thickness and any other adnexal pathology . If the endometrial thickness ≥10mm in USG , endometrial biopsy was done . Viscosmi formula was used for the measurement of uterine volume that is $4/3\pi \times W/2 \times L/2 \times T/2$. In case of multiple fibroids, volume of largest fibroid was calculated .

Mifepristone 25mg/day was given orally to all the subjects for a duration of 3 months . patients were followed up at the end of 3 months and at the end of 6 months i.e.,3 months after stopping therapy to look for recurrence of symptoms or regrowth of fibroid .

RESULTS & OBSERVATIONS :

Out of 50 patients under observation majority were in the age group of 31-40yrs with mean age of 35.48 ± 7.39 years with mean BMI 26.10 ± 3.59. Majority were para 2 . Most common symptom was menorrhagia(86%) followed by dysmenorrhoea(76%) and pain abdomen(52%), lump abdomen(14%), infertility(6%), urinary symptoms(6%).

Intramural type of fibroid was the most common found in 58% of the cases ; followed by subserosal in 26% and submucosal in 16% of the patients

Table No 1: Showing changes in the mean values & percentage change of various parameters .

Before treatment		At the end of 3 months		At 6 months	
Menorrhagia (PBAC)	253.8 ± 164.79	8.8 ± 24.96	96.53% decrease	86.72 ± 75.44	65.83% decrease
Dysmenorrhea (VAS)	4.04 ± 2.08	0.76 ± 1.45	81.18% decrease	2.84 ± 2.17	29.7% decrease

Abdominal pain(VAS)	2.56 ± 2.28	0.72 ± 1.44	71.87% decrease	1.48 ± 2.01	42.18% decrease
Uterine volume	183.18 ± 119.7cc	151.31 ± 87.75	17.39% decrease	152.87 ± 104.53cc	16.54% decrease
Endometrial thickness	6.17 ± 2.23mm	8.47 ± 3.3	37.16% increase		
Fibroid volume	64.66 ± 68.46cc	44.87 ± 51.62	30.69% decrease	37.1 ± 50.63cc	42.49% decrease
Hemoglobin	9.96 ± 1.17gm/dl	10.88 ± 0.84	8.46% increase	10.96 ± 0.90gm/ dl	10.04% increase

84.61% patients remained amenorrhoeic after the treatment . In this study patients regained their menstruation in a mean duration of 32.38 ± 11.74 days after the stopping the drug

ENDOMETRIAL HISTOPATHOLOGY:

Before treatment 4 patients(8%) and after treatment 17 patients(34%) showed endometrial thickness ≥ 10mm . Proliferative endometrium was the most common finding after treatment Among 50 patients, none of them had any major side effects. Nausea was most common seen in 12% of the patients. Backache, hotflushes and increased liver enzymes were seen in 6% each.

DISCUSSION:

In the present study, the mean age of study population is 35.48 ± 7.39 years that is comparable to observations by Sikha Seth et al6 which is 38.47 ± 4.9. Majority of the women were parous , most being para 2 (32%). According to Aamir T Khan et al7 , parity is inversely associated with risk of fibroid development.

Table 2 : Decrease in PBAC & VAS scores at the end of treatment in various studies :

Study	Sample size	Dosage	Duration	Decrease in PBAC score	Percentage decrease in VAS
Engman et al 20098		50 mg alternate day	3 months	100 %	
Kulshrestha et al 9		25 mg/day	3 months	96.4 %	
Kulshrestha et al 9		10 mg/day	3 months	92.4 %	
Seema Saharan et al 10	25	10 mg/day	3 months	98 %	79%
Anupama et al 11	50	25 mg/day	3 months	95.6 %	87.5%
Carbonell et al12	71	2.5mg/day			70%
Carbonell et al12	75	5mg/day			85.7%
Our study	50	25 mg/day	3 months	96.53 %	81.18%

Reduction in PBAC score is due to suppressive effect of RU486 on endometrial vasculature by acting on VEGF. Decrease in PBAC is almost same in all the above studies. Engman et al8 showed 100% decrease in PBAC . Study conducted by Anupama et al 11 showed a maximum decrease in VAS percentage that is 87.5 . 84.61% patients in the present study had amenorrhoea at the end of 3 months. With increase in the duration of treatment, the percentage of people who were amenorrhoeic had decreased . This might be because of increased rates of breakthrough bleeding or spotting [13]

None of the patients were amenorrhoeic at the end of followup . Menstruation was resumed in a mean duration of 32.38 ± 11.74 days The mean hemoglobin concentration in the present study , before treatment is 9.96 ± 1.17 gm/dl which is more than other studies like Seema Saharan et al 10 , Sikha seth et al 6 and Rita lal et al 14 . Our study values coincide with the study of Anupama et al 11 which shows mean hemoglobin 9.96 ± 1.15 gm/dl . Our study value is less when compared to that of Engman et al 8 and Carbonell et al 12 whose values are 12.1 ± 5 and 11.0 ± 2 respectively . In our study there was 10.06 % increase in hemoglobin percentage at the end of 6 months . This could be due to decreased menstrual flow even in the followup phase

Table 3 : Showing decrease in uterine and fibroid volume of various studies at the end of treatment

Study	Dose	Duration of treatment	Decrease in uterine volume	Decrease in fibroid volume
Shikha seth et al6	25mg/day	3 months	36.3 %	46.38%
Anupama et al 11	25mg/day	3 months	34.3 %	51.2%
Engman et al 8	50 mg alternate day	3 months	0 %	27%
Carbonell et al 12	2.5mg/day	3 months	18.2 %	27.9%
Carbonell et al 12	5mg/day	3 months	22.1 %	46.4%
Eisinger et al 15	5 mg/day	6 months	48 %	
Eisinger et al 15	10mg/day	6 months	49 %	
Bagaria et al 16	10mg/day	3 months	26.6%	
Kulshrestha et al9	25mg/day	3 months		35.7%
Kulshrestha et al9	10mg/day	3 months		22.5%
Our study	25mg/day	3 months	17.39%	30.69%

In the present study there is decrease of 16.54 % in uterine volume compared to the pre-treatment volume .There was only marginal increase in uterine volume at the end of followup when compared to post-treatment indicating that the decrease in uterine volume almost sustained at the end of 6 months. In our study there was 42.49 % decrease in fibroid volume at the end of 3 months post-treatment followup which indicates that even after the drug was stopped its effect continued in the post-treatment phase . Difference in various studies might be due to inter observer variability and variation in population under study .

ENDOMETRIAL THICKNESS AND HISTOPATHOLOGY :

In the present study, the increase in endometrial thickness seen might be due to unopposed estrogenic effect on the endometrium by mifepristone. 34% of the patients showed endometrial hyperplasia after treatment and most common type was proliferative endometrium which is comparable to the study conducted by Kulshrestha et al9. There were no atypical or malignant changes in our study. Proliferative endometrium is the most common HPE finding in our study(52.9%) which is comparable to Kulshreshta et al9(53.5%). Secretory endometrium seen in 29.4% and cystic glandular hyperplasia seen in 17.6% .

SURGICAL INTERVENTION :

In our study , 5 patients out of 50 , which is 10 % underwent surgery after completion of 6 months . 3 subjects underwent hysterectomy and 2 underwent myomectomy .

Patients who underwent TAH had menorrhagia and their PBAC score after the followup was > 100 . There was minimal change in their uterine and fibroid volumes at the end of followup when compared to the pre-treatment value. While these patients had reduced intensity of symptoms during treatment with mifepristone .

Patients who underwent myomectomy complained of dysmenorrhea with VAS score 6 . Though there was significant decrease in uterine and fibroid volume , patients were taken up for surgery due to their persisting symptom .

In study by Sikha seth et al 6 6 out of 93 patients underwent hysterectomy as they did not respond to medical treatment and fibroid volume was increased .Total incidence of hysterectomy in this study was 12.1 % .

In study conducted by Anupama et al 11 5 patients underwent hysterectomy which is comparable to our study .

In Carbonell et al 12 study , prior to the termination of 3 months of treatment , in 5 mg group , out of 110 patients 1 patient underwent hysterectomy due to menorrhagia . In 2.5mg group , out of 110 patients , 3 patients underwent hysterectomy due to menorrhagia .

SIDE EFFECTS:

In our study nausea was noted in 12%, hotflushes , increased liver transaminases and backache in 6% each.

Vidhushi kulshrestha et al 9 reported leg cramps 10% , hot flushes 7.1% , weakness 7.1% and palpitations 1.4 % more commonly in the 25mg group compared to the 10mg group . Transient rise in LFT was seen in 2.8% and 2.7% of patients in 25mg and 10mg group respectively .

Study by Rita lal et al 14 reported hotflushes in 8% and Carbonell et al 12 reported vomiting , fatigue , nausea and hot flushes .
In none of the above studies , there were major side effects and so the compliance to drug treatment was good in almost all studies including the present study .

CONCLUSION:

- Most common symptom was Menorrhagia followed by Dysmenorrhoea.
- From the present study it can be concluded that at the end of 3 months, there was significant reduction in the amount of menorrhagia , dysmenorrhea , abdominal pain , uterine and fibroid volume and improvement in haemoglobin level .
- There were minimal tolerable side effects like , nausea , backache , hotflushes and increased liver transaminases , which was the major reason for good patient compliance .
- Increase in endometrial thickness was noted at the end of the treatment but endometrial biopsy did not show any evidence of atypia or malignancy
- Surgical intervention was required at the end of 6 months due to persistence of symptoms in 10% of the cases .
- 84.61% reported amenorrhoea at the end of the treatment and menstruation was resumed in a mean duration of 32.38 ± 11.74 days .
- Thus the results of present study shows that Mifepristone can be offered as a good treatment option in uterine fibroids.

REFERENCES :

1. Adamson GD. Treatment of uterine fibroids: Current findings withgonadotropin-releasing hormone agonists. American Journal of Obstetrics & Gynecology. 1992 Feb 1;166(2):746-51.
2. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. American journal of obstetrics and gynecology. 2003 Jan 1;188(1):100-7.
3. Sankaran, S., & Manyonda, I. T. (2012). Medical management of fibroids Best practice and Research clinical Obstetrics and gynecology, 22(4)
4. Narvekar N, Critchley HO, Cheng L, Baird DT. Mifepristone-induced amenorrhoea is associated with an increase in microvessel density and glucocorticoid receptor and a decrease in stromal vascular endothelial growth factor. Human Reproduction. 2006 Jun 28;21(9):2312-8.
5. Spitz IM. Mifepristone: where do we come from and where are we going?: Clinical development over a quarter of a century. Contraception. 2010 Nov 1;82(5):442-52.
6. Seth S, Goel N, Singh E, Mathur AS, Gupta G. Effect of mifepristone (25 mg) in treatment of uterine myoma in perimenopausal woman. Journal of mid-life health. 2013 Jan;4(1):22.
7. Khan AT, Shehmar M, Gupta JK. Uterine fibroids: current perspectives. International journal of women's health. 2014;6:95.
8. Engman M, Granberg S, Williams AR, Meng CX, Lalitkumar PG, Gemzell-Danielsson K. Mifepristone for treatment of uterine leiomyoma. A prospective randomized placebo controlled trial. Human Reproduction. 2009 Apr 23;24(8):1870-9.
9. Kulshrestha V, Kriplani A, Agarwal N, Sareen N, Garg P, Hari S, Thulkar J. Low dose mifepristone in medical management of uterine leiomyoma-an experience from a tertiary care hospital from north India. The Indian journal of medical research. 2013 Jun;137(6):1154.
10. Saharan S, Khajotia S, Falodia S, Budania S, Prakash P. Effect of Mifepristone on Uterine Fibroid with special reference to Symptoms and its Size. Int multispeciality J health. 2016.
11. Anupama Hari, Sruhya M . A Prospective and Interventional Study of the Role of Low Dose Mifepristone in the Management of Uterine Leiomyoma in Perimenopausal Women .Saudi Journal of Medical and Pharmaceutical Sciences, 2017; 3(10B):1088-1096
12. Carbonell JL, Acosta R, Pérez Y, Garcés R, Sánchez C, Tomasi G. Treatment of uterine myoma with 2.5 or 5 mg mifepristone daily during 3 months with 9 months posttreatment followup: randomized clinical trial. ISRN obstetrics and gynecology. 2013 Jul 29;2013.
13. Murphy AA, Kettel LM, Morales AJ, Roberts VJ, Yen SS. Regression of uterine leiomyomata in response to the antiprogesterone RU 486. The Journal of Clinical Endocrinology & Metabolism. 1993 Feb 1;76(2):513-7.
14. Lal R, Ashwini A, Lal S. Role of low dose mifepristone in the treatment of symptomatic fibroid uterus: a double control randomized control trial. JOURNAL OF EVOLUTION OF MEDICAL AND DENTAL SCIENCES-JEMDS. 2015 Jul 16;4(57):9990-10000
15. Eisinger SH, Meldrum S, Fiscella K, le Roux HD, Guzick DS. Low-dose mifepristone for uterine leiomyomata. Obstetrics & Gynecology. 2003 Feb 1;101(2):243-50.